REMARKS

I. Preliminary Remarks Regarding Amendment

The Applicants would like to thank Examiner Elizabeth Slobodyansky for the telephone interview of May 21, 2003 with William K. Merkel and Lynn L. Janulis, and for her helpful comments.

The foregoing amendment is in the revised amendment format as provided in 1267 OG 106. Accordingly, the provisions of 37 C.F.R. § 1.21, requiring submission of clean and marked-up versions of the replacement paragraphs and claims, should be waived. A clean copy of the pending claims after entry of the amendment is attached hereto as **Appendix A**, as a convenience to the Examiner.

The Applicants do not intend by any amendments to abandon the subject matter of any claim previously presented. The Applicants reserve the right to pursue the subject matter of such claims during prosecution of this or subsequent applications. Claims 1-8, 10, 11, 46-48, and 59-64 are pending and currently being examined. Claims 1-4, 8, 10, 46, 48, 59, and 61-62 are amended herein; new claim 65 is added herein. Thus, claims 1-8, 10, 11, 46-48, and 59-65 will be pending upon entry of the present amendment.

The Applicants have noted the Examiner's objection under 35 U.S.C. 132 to the amendment filed September 18, 2002, asserting that it introduced new matter into the disclosure. The Applicants respectfully traverse this objection and submit that the amendment adequately described the originally filed amino acid position numbering in the sequence listing, and further submit that the Applicants amended the numbering scheme in Example 9 (pages 96-97) of the specification accordingly.

The human E3αI ubiquitin ligase (huE3αI) SNP is correctly set out in Example 9 as SEQ ID NO: 18 (p. 96, lines 24-29). However, after comparing the sequence of the single nucleotide polymorphism (SEQ ID NO: 18) to SEQ ID NO: 1, it would be apparent to the reader that there were some typographical errors in the written comparisons of the sequences (p. 96, lines 29-33 and p. 97, lines 9-12), and the corrections would also be apparent. First, SEQ ID NO: 17, as mentioned at line 10 of p. 97 of the original specification, is not the sequence of a huE3αI SNP. SEQ

Received from < 3124741159 > at 5/27/03 9:43:31 PM [Eastern Daylight Time]

ID NO: 17 is a 15-amino-acid artificial sequence. The correct sequence for the huE3αI SNP is SEQ ID NO: 18 as provided in the application as filed. Second, a comparison of the sequences of SEQ ID NO: 18 with SEQ ID NO: 1 would reveal that the single nucleotide difference is a thymidylate at position 4657 of SEQ ID NO: 18 and a cytidylate at that position in SEQ ID NO: 1 (not at position 4702). Third, the single nucleotide polymorphism at position 4657 would result in a change of an arginine to a tryptophan residue at position 1568 in SEQ ID NO: 19 (not at position 1508). The Applicants have enclosed sequence comparisons (See **APPENDIX B**; BLAST 2 SEQUENCES program of the National Center for Biotechnology Information, NIH) of the polynucleotide sequences of SEQ ID NOS: 1 and 18 and the polypeptide sequences of SEQ ID NOS: 2 and 19 to confirm that there was no new matter introduced by the previous amendment. The amendment simply corrected typographical errors in sequence identification numbering in Example 9.

New claim 65 is drawn to an isolated nucleic acid molecule comprising a nucleotide sequence that exhibits a single nucleotide polymorphism relative to SEQ ID NO: 1 of the instant application. Claim 65 finds support in the specification (see Example 9, page 97, line 23 through page 98, line 12). Thus, at a minimum, the specification provides written descriptive support for two alleles of human E3α ubiquitin ligase: two polynucleotides (SEQ ID NOS: 1 and 18) which encode two polypeptides (SEQ ID NOS: 2 and 19, respectively).

The Applicants have noted the Examiner's objection to claims 1-3 because of the omission of the word "and" between the terminal clauses of claims 1-3; and have amended the claims accordingly. Thus, the objection may properly be withdrawn.

The foregoing amendment to the claims includes no new matter.

II. Patentability Remarks

A. The Rejections Under 35 U.S.C. 112, First Paragraph, for Lack of Written Description Should Be Withdrawn

The Examiner rejected claims 2-8, 10, 11, 46-48, and 59-64 under 35 U.S.C. § 112, first paragraph, for assertedly lacking adequate written description. The

Received from < 3124741159 > at 5/27/03 9:43:31 PM [Eastern Daylight Time]

Examiner provided the following reasons for rejection: 1) claim step 2(b) and claim 59 do not provide sufficient structural support for the claimed genus; 2) claim 3 lacks a limit on the number of amino acid modifications that may be encoded by the claimed DNAs; and 3) claims 4-8, 10, 11, 46-48, and 60-64 depend from claims 1-3 and are therefore rejected for the same reasons the base claims have been rejected. The Applicants respectfully disagree with the basis for this rejection and submit that the claims, as originally filed, are adequately described in the specification.

The basis asserted for this rejection, however, is now moot in consideration of the amendment to the claims. To expedite prosecution, the Applicants have amended claims 2-3 and 59 to describe a recited sequence relationship to SEQ ID NO: 2 and a combination of structural and/or functional limitations which render the basis for rejection moot.

The Applicants have amended claim 2 to recite "a nucleotide sequence encoding a polypeptide that is at least 90 percent identical to the polypeptide set forth in SEQ ID NO: 2, wherein the encoded polypeptide has at least 1,649 amino acids and has human E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 2," thus providing structural and functional characteristics sufficient to identify members of the claimed genus. Support in the specification for a human E3α ubiquitin ligase polypeptide that comprises less than the full-length amino acid sequence of human E3α ubiquitin ligase I of SEQ ID NO: 2 is found at page 16, line 30 through page 17, line 13. There is written descriptive support for truncations and/or deletions comprising up to about, or more than about, 100 amino acids. SEQ ID NO: 2 is 1,749 amino acids in length. Thus, there is literal support for amino acid sequences of at least 1,649 amino acids in length. Likewise, support in the specification for human E3α ubiquitin ligase activity is found at page 2, line 8 through page 4, line 14. The specification describes how E3α ubiquitin ligase functions in the proteosomal pathway.

The Applicants have amended claim 3 to recite a nucleotide sequence encoding a polypeptide set forth in SEQ ID NO: 2 with modifications "of one to 100 amino acids selected from the group consisting of amino acid substitutions, amino

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Received from < 3124741159 > at 5/27/03 9:43:31 PM [Eastern Daylight Time]

acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the polypeptide has human E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 2," thus providing structural and functional characteristics sufficient to identify members of the claimed genus. Support in the specification for variants of human E3α ubiquitin ligase polypeptide with modifications of from one to 100 amino acids is found at page 17, lines 14-32. Likewise, support in the specification for human E3α ubiquitin ligase activity is found at page 2, line 8 through page 4, line 14. The specification describes how E3α ubiquitin ligase functions in the proteosomal pathway. Applicants submit that amended claim 3 puts the skilled person in possession of the attributes and features of each species in the claimed genus.

The Applicants have amended claim 59 to depend on amended claims 1 to 3. Likewise, claims 4-8, 10, 11, 46-48, and 60-64 depend on amended claims 1-3. Amended claims 1-3 are supported by an adequate written description. Each of the limitations added in dependent claims 4-8, 10, 11, 46-48, 59, and 60-64 is supported by an adequate written description and the Examiner has not challenged that position. Accordingly, these amended claims are supported by an adequate written description under U.S.C. § 112, first paragraph.

Consequently, the rejection of claims 2-8, 10, 11, 46-48, and 59-64 for lack of written description, are rendered moot by amendment, and the rejection should be withdrawn; moreover, a rejection of new claim 65 on the same ground would be improper.

Received from < 3124741159 > at 5/27/03 9:43:31 PM [Eastern Daylight Time]

B. The Rejections Under 35 U.S.C. § 112, First Paragraph, for Lack of Enablement Should Be Withdrawn

Claims 3-8, 10, and 46-48 were rejected under 35 U.S.C. § 112, first paragraph, for assertedly not enabling the full scope of the claims, which were asserted to encompass modifications and fragments of unknown structures. The Applicants respectfully disagree and submit that the claims, as originally filed, are enabled by the specification.

This rejection is now moot, however, in view of the amendment to the claims. The Applicants have amended claim 3 by defining the claimed sequences with a combination of structural and/or functional characteristics that are enabled by the specification. For example, the variants of claim 2 all possess a recited sequence relationship to SEQ ID NO: 2 and retain human E3α ubiquitin ligase activity. The application teaches one how to make and use such variants without undue experimentation.

The Applicants have amended claim 3 to recite a nucleotide sequence encoding a polypeptide set forth in SEQ ID NO: 2 with modifications "of one to 100 amino acids selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the polypeptide has human E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 2." Support in the specification for variants of human E3α ubiquitin ligase polypeptide with modifications of from one to 100 amino acids is found at page 17, lines 14-32. Likewise, support in the specification for human E3α ubiquitin ligase activity is found at page 2, line 8 through page 4, line 14. The specification describes how E3α ubiquitin ligase functions in the proteosomal pathway. Given the base sequence information (e.g., SEQ ID NO: 2), the specifically identified activity of the molecules, and the well-known techniques for detecting such activity, the Applicants submit that one skilled in the art would be able to identify, and make, the claimed variants of the native human E3α ubiquitin ligase using no more than routine experimentation.

Received from < 3124741159 > at 5/27/03 9:43:31 PM [Eastern Daylight Time]

The Applicants submit that they have satisfied the enablement requirement by providing sufficient disclosure to teach one of skill in the art how to make and use the claimed invention without requiring undue experimentation. The statute does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 176 U.S.P.Q. 331, 333 (C.C.P.A. 1973). Furthermore, what constitutes undue experimentation depends upon a number of factors, which include the quantity of experimentation necessary, the nature of the invention, the amount of direction or guidance presented, the presence of working examples, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. and Int'f (1986); *see also* In re Wands, 8 U.S.P.Q.2d 1400 (Fed. Cir. (1988)).

In the instant case, the quantity of experimentation would be insignificant because the Applicants have taught the reference polynucleotide sequence in SEQ ID NO: 1 and the reference amino acid sequence in SEQ ID NO: 2. Moreover, modifications in the form of substitutions, deletions and/or insertions are amenable to any of a wide number of well-known molecular techniques and the Applicants have taught the function (i.e., activity) that would provide a basis for designing a variety of assays to identify variants having the requisite activity.

The preceding discussion also establishes that the Applicants have provided considerable guidance in identifying sequences related to the reference sequences and have identified an activity associated with such molecules. This guidance, coupled with the knowledge in the art, provides sufficient direction to allow one of skill to construct, test and identify (i.e., make), as well as use, the claimed molecules. Consistent with this guidance, the Applicants have disclosed a working example of a variant exhibiting the polynucleotide sequence set forth in SEQ ID NO: 18, which encodes a polypeptide having the amino acid sequence set forth in SEQ ID NO: 19. Another factor weighing in favor of concluding that the claims are enabled is the relative skill of those in the art, which is generally recognized as being quite high. Finally, the Applicants submit that the breadth of the claims also favors a determination that the claims are enabled because claim breadth reasonably correlates to the scope of the disclosure in addressing particular human E3α ubiquitin ligase

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Received from < 3124741159 > at 5/27/03 9:43:31 PM [Eastern Daylight Time]

polynucleotides, and the polypeptides encoded thereby. The claims are limited to similar structures that encode or exhibit a particular enzymatic activity characteristic of a specific protein, human E3α ubiquitin ligase.

For the foregoing reasons, the Applicants submit that the claims, as amended, are enabled and the rejection of claims 3-8, 10, and 46-48 under 35 U.S.C. § 112, first paragraph, for lack of enablement, has been overcome and should be withdrawn. Analogously, a rejection of new claim 65 on the same ground would be improper.

C. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 2-8, 10, 11, 46-48, and 59-64 were rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as their invention. Specifically, the claims were rejected for not defining the specific function of "human E3α ubiquitin ligase activity." The Applicants respectfully traverse this rejection.

The specification specifically states that "E3α enzyme binds directly to the primary destabilizing N-terminal amino acid and catalyzes ubiquitin conjugation thereby targeting the protein for degradation." (See the specification at p. 2, lines 23-25). The specification also states that "huE3α polypeptides are intracellular enzymes that control protein conjugation and degradation." (See the specification at p. 3, lines 21-22). The specification also discloses that "E3α plays a role in the overall increase in ubiquitination that is associated with and may mediate muscle atrophy in catabolic and other disease states." (See the specification at p. 4, lines 4-6). The application further discloses structures that correlate to this specific function. The specification discloses that the E3α family is a distinct family characterized by the existence of high similarity regions (I-V). (See the specification at p. 2, line 27 to p. 3, line 8.)

For these reasons, the rejection of claims 2-8, 10, 11, 46-48, and 59-64 under 35 U.S.C. § 112, second paragraph, for indefiniteness should be withdrawn, and a rejection of new claim 65 on the same ground would be improper.

Received from < 3124741159 > at 5/27/03 9:43:31 PM [Eastern Daylight Time]

D. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Patent Office also rejected claims 2-8, 10, 11, 46-48, and 59-64 under 35 U.S.C. § 102(b) as assertedly being anticipated by each of the following references:

1) Hillier *et al.* for teaching an EST of 682 bp that is 99.3% identical to SEQ ID NO: 1 and that encodes an ubiquitin protein ligase E3 component (Genbank Accession No. AI929033);

2) Strausberg *et al.* for teaching an EST of 641 bp that is 99.5% identical to SEQ ID NO: 1 and that encodes an ubiquitin protein ligase E3 component (Genbank Accession No. AI361043); and

3) Varshavsky *et al.* (hereinafter Varshavsky) for teaching murine UBR1, which is 70.3% identical to SEQ ID NO: 1.

To anticipate claimed subject matter under 35 U.S.C. § 102, a single reference must identify each and every feature recited in the claim. M.P.E.P. § 2131. The Applicants submit that none of Hillier *et al.*, Strausberg *et al.*, or Varshavsky disclose each limitation of any of the rejected claims as amended.

The ESTs of Hillier *et al.* and Strausberg *et al.* fail to encode a polypeptide "that is at least 90 percent identical to the polypeptide set forth in SEQ ID NO: 2, wherein the encoded polypeptide has at least 1,649 amino acids and has human E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 2," as recited in claim 2. Likewise, the ESTs of Hillier *et al.* and Strausberg *et al.* fail to encode a polypeptide set forth in SEQ ID NO: 2 with modifications "of one to 100 amino acids selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the polypeptide has human E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 2," as recited in claim 3. The ESTs of Hillier *et al.* and Strausberg *et al.* are smaller than 1,649 amino acids in length and therefore cannot disclose an encoded polypeptide that has at least 1,649 amino acids and possesses the claim-recited specific activity. Moreover, because claim 59, as amended, depends on any of claims

Received from < 3124741159 > at 5/27/03 9:43:31 PM [Eastern Daylight Time]

1-3, Hillier *et al.* and Strausberg *et al.* fail to anticipate the subject matter of this claim.

Similarly, the murine UBR1 sequence of Varshavsky fails to disclose a polypeptide having an amino acid sequence that is 90% identical to the amino acid sequence set forth in SEQ ID NO: 2, as recited in claim 2. Thus, the Varshavsky sequence does not anticipate the subject matter of any of the claims as amended.

For these reasons, the rejections of claims 2-8, 10, 11, 46-48, and 59-64 under 35 U.S.C. § 102(b) have been rendered moot and should be withdrawn.

Received from < 3124741159 > at 5/27/03 9:43:31 PM [Eastern Daylight Time]

III. Conclusion

In view of the foregoing amendment and remarks, the Applicants submit that the claims are in condition for allowance and early notification thereof is respectfully requested. Should the Examiner wish to discuss any aspect of the present application, she is urged to contact the undersigned at the telephone number indicated.

Respectfully submitted,

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Received from < 3124741159 > at 5/27/03 9:43:31 PM [Eastern Daylight Time]